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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,428	06/26/2006	Paolo Farina	833-135 US	9498

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,428	FARINA ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-10 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 09152005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casper et al. Cancer Chemother Pharmacol (1985), Vol. 15, pages 233-235 (Casper), Barai et al. Helvetica Chimica Acta (2002), Vol. 85, pages 1893-1900 (Barai), Utagawa Journal of Molecular Catalysis B: Enzymatic 6 (1999) pages 215-222 (Utagawa), and Konno et al. US 7,132,409 (Konno) in combination.

Claims 1-9 are drawn to a process for the preparation of fludarabine phosphate (I) comprising: a) reaction of 2-fluoradenine with 9-β-D-arabinofuranosyl-uracil in the presence of *Enterbacter aerogenes* to give crude fludarabine (II); b) treatment of crude fludarabine with acetic anhydride to give 2', 3', 5'-tri-O-acetyl-9-β-D-arabinofuranosyl-2-fluoroadenine (III); c) hydrolysis and crystallization of compound (III) to give fludarabine (II); d) phosphorylation of fludarabine to give fludarabine phosphate (I). Claim 10 is drawn to a fludarabine phosphate salt with organic amines or with ammonia.

Casper teaches that F-ara-AMP (fludarabine phosphate) is an adenosine analogue that is resistant to deamination; it is a more potent cytotoxic compound than ara-A in experimental tumor systems (page 233). Ara-A (9-β-D-arabinofuranosyladenine) is one of several adenosine analogue possessing antiviral and antitumor activity. The clinical use of this drug as an antineoplastic agent is limited, however, by its rapid hydrolysis to ara-H (9-β-D-arabinofuranosylhypoxanthine) via adenosine deaminase.

Casper differs from the instantly claimed invention in that Casper does not teach a synthetic protocol.

Barai teaches that pentofuranosyl nucleosides of 2,6-diaminopurine are valuable precursors for the preparation of a broad range of base (guanine, isoguanine, 2-haloadenines, etc.) and sugar-modified analogues of natural nucleosides (page 1893). Among these analogues, some are recognized as very effective agents against lymphoproliferative disorders and hematologic malignances such as fludarabine. Chemical synthesis of 2,6-diaminopurine nucleosides are based on a convergent approach, and the transformations of purine bases of natural nucleosides are multi-step processes and rather laborious. On the contrary, enzymatic synthesis of purine nucleosides with pyrimidine nucleosides as donors of the carbohydrate moiety in the reaction of an enzymatic transglycosylation of purine bases have been shown to represent an expedient alternative to chemical methods. The approach offers obvious advantages over chemical procedures and consists in the concerted biochemical reactions catalyzed by cytidine deaminase (CDase), uridine phosphorylase (UPase), and purine nucleoside phosporylase (PNPase).

Utagawa teaches that microbial enzymes, as a biocatalyst in the chemical process, have been applied to the synthesis of stereo-specific nucleosides (pages 216). Microbial enzymes that catalyze trans-arabinosylation reaction have been looked for and applied in the chemical process to produce ara-A from uridine as shown in Fig. 1. Uracil arabinoside (ara-U) can be prepared from uridine through chemical reaction with ethylene carbonate followed by the hydrolysis of cyclouridine (cyclo-U) by acid. *Enterobacter aerogenes* was selected as the best producer of ara-A and subjected to further study. The optimal temperature and pH for ara-A synthesis were 60-65 C and

7.0, respectively. The reaction temperature is very important and a key to the synthesis of ara-A. A high reaction temperature has advantages such as preventing from contamination of other bacteria during the reaction process and increasing the substrate solubility in the reaction mixture, following by accelerating the reaction (page 217).

Konno teaches that in the separation of target adenosine derivatives from the obtained reaction mixture, preferably, neutralization, salt formation reaction, or any other suitable reaction is performed, to thereby obtain the target compound transformed into a phosphate or phosphate salt (column 3). Through a suitable combination of neutralization and salt formation reaction, the target compound of high purity can be obtained. The reaction is reacted with an organic amine, to thereby form an organic amine salt of the target compound, and then the salt is separated

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce fludarabine phosphate by the instantly claimed method. Barai teaches that the enzymatic synthesis of purine nucleosides with pyrimidine nucleosides as donors of the carbohydrate moiety in the reaction of an enzymatic transglycosylation of purine bases have been shown to represent an expedient alternative to chemical methods. The approach offers obvious advantages over chemical procedures and consists in the concerted biochemical reactions catalyzed by cytidine deaminase (CDase), uridine phosphorylase (UPase), and purine nucleoside phosporylase (PNPase). It would have also been obvious to employ *Enterobacter aerogenes* as the enzymatic catalyst since it tolerates high-temperature reactions. A high reaction temperature has advantages such as preventing from contamination of other bacteria

during the reaction process and increasing the substrate solubility in the reaction mixture, following by accelerating the reaction. Purification steps such the addition of acetyl groups and recrystallization are routine and well within the purview the skilled artisan. As shown by Konno, it would have also been obvious to employ an organic amine to aid in the purification of the phosphate salts.

Conclusion

5. Claims 1-10 are pending. Claims 1-10 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dr. Patrick T. Lewis
Primary Examiner
Art Unit 1623

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